Treatment of Decompression Sickness in Swine with Intravenous Perfluorocarbon Emulsion

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Background: We examined an adjunctive treatment for severe decompression sickness (DCS) to be used when hyperbaric treatment is delayed or unavailable. **Hypothesis:** It has been hypothesized that intravenous perfluorocarbon (PFC) emulsion combined with 100% inspired O_2 would improve the outcome in severe DCS. **Methods:** Swine (n = 45) were compressed to 4.9 ATA on air for 22 h and brought directly to 1 ATA at $0.9 \text{ ATA} \cdot \text{min}^{-1}$. The animals were then randomized to three groups. The first group breathed ambient air, the second group breathed 100% O_2, and a third group received $6 \text{ ml} \cdot \text{kg}^{-1}$ of perflubron emulsion (Oxygent™) intravenously and breathed 100% O_2. Outcomes of neurological and cardiopulmonary DCS and death were recorded. **Results:** Animals that received PFC emulsion sustained less DCS (p < 0.01) than the other groups (53% vs. 93%). No animals in the PFC group sustained neurological DCS, which was present in 69% of the subjects in the other two groups. **Conclusion:** O_2 breathing postdive did not significantly reduce morbidity or mortality in this model. Postdive treatment with PFC emulsion and 100% O_2 decreased the incidence of DCS after nonstop decompression from saturation.
Keywords: DCS, saturation diving, perfluorochemicals, steroids.

DESPITE THE KNOWN dangers, there are plausible situations that may require humans to conduct a rapid decompression following inert gas saturation in hyperbaric conditions. U.S. Navy submarines rarely experience accidents that leave their ships disabled, but when they do, they pose a difficult rescue problem. Submarines are maintained at normal atmospheric pressure, but over time the pressure within a disabled submarine is expected to rise due to a variety of factors. While awaiting rescue, the sailors' tissues will most likely become saturated with N_2 from breathing air at elevated ambient pressure. Rescue efforts may not allow a proper, controlled decompression, and ready access to a hyperbaric chamber cannot be guaranteed. Similarly, in aviators and astronauts, comparable situations may arise during explosive decompressions or emergency extravehicular activities. During a mission, they face the same potential problems as sailors with limited availability of adequate treatment assets. Decompression sickness (DCS) sustained in such situations could potentially cause severe long-term morbidity and mortality. Accordingly, there is great interest in prophylactic or adjunctive treatments for severe DCS that can be used when hyperbaric treatment is delayed or unavailable.

We previously developed a dose-response curve for large animals to describe the natural history after such exposures and provide a platform for intervention testing (4). The present study describes experiments using Oxygent™, an intravenous (IV) perfluorocarbon emulsion, as a therapeutic agent for severe DCS in the event of delayed or unavailable hyperbaric treatment. Developed as inert insulating materials as part of the Manhattan Project during World War II, liquid perfluorochemicals (PFCs) are synthetic "oils" made up of polyfluorinated carbon chains. In the mid-1960s, it was discovered that PFCs could dissolve and transport large quantities of non-polar gases, including O_2 and N_2. Indeed, in 1966, Clark and Gollan demonstrated the biological application of PFCs by showing that a PFC-submerged rodent could survive while breathing unemulsified oxygenated liquid PFCs (2). Several first generation PFC emulsions, such as Fluosol DA, were beleaguered with pharmacological (i.e., complement activation), and logistical problems that resulted in their removal from market use. Oxygent™ (60% weight per volume perflubron-based emulsion, Alliance Pharmaceutical Corp., San Diego, CA.), is a second generation PFC emulsion with good safety and tolerability that is approximately three times as concentrated as Fluosol. Compared with normal saline, Oxygent™ carries 15 times as much oxygen and 20 times as much nitrogen per unit volume (6). Oxygent™ is currently in phase III clinical studies for use as a temporary blood substitute based on its O_2-carrying capacity. However, the substance's high affinity for N_2 makes it potentially useful for treating diving casualties.

Previous studies of PFC emulsion treatment of DCS in small animals have demonstrated beneficial effects. Novotny et al. reported that PFC emulsion accelerated

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elimination of inert gas from canine muscle tissue by 110% over that in saline-treated dogs (14). Hamsters showed significant increased survival, reduced bubble formation, and fewer cardiac arrhythmias when they were infused IV with PFC emulsion after a hyperbaric excursion (11,18). Spiess et al. (18) reported that after a decompressive insult, 67% of rats given PFC emulsion and 100% O_2 survived compared with only 8% given an equivalent volume of hetastarch. PFC emulsion administration has been shown to increase survival after iatrogenic air embolism in rabbits, and other studies indicate cerebral protection from venous air embolism in a cardiac bypass model (8,9,15–17,21). These studies showed not only a decreased incidence of cerebral air embolism, but decreased infarction size and preservation of neuronal function.

There have been highly promising results of PFC treatment for DCS in small animals with relatively high metabolic rates and rapid gas exchange kinetics. However, no study yet has examined the treatment potential for severe DCS in a large-animal model approximating humans. In this study, we assess the treatment effect of perflubron emulsion infusion combined with 100% inspired O_2 on DCS in a large-animal model after nonstop decompression from saturation conditions, a scenario possible in certain military disasters.

METHODS

All procedures were conducted in accordance with National Research Council guidelines on laboratory animal use (2). Before commencing, the Institutional Animal Care and Use Committee reviewed and approved all aspects of this protocol. The institutional animal care facility is fully AALAC accredited.

Subjects: Neutered male Yorkshire swine littermates (n = 45, mean weight 20.9 kg $\pm$ 0.2 SEM) were examined by a veterinarian on receipt, then fitted with an adjustable chest harness and housed in individual runs where water was freely available. Their daily feedings consisted of 2% by body weight of laboratory animal feed (Harlan Teklad, Madison, WI). Animals remained in the care facility for a minimum of 72 h adjusting to their new surroundings before experiments.

Predive preparation and dive protocol: Animals were handled and prepared as described previously (4). For each experiment, three animals were used. After recovering from surgical catheterization of a peripheral vein, the three subjects underwent a dry chamber dive to 4.9 ATA for 22 h, then decompressed to 1 ATA at 0.9 ATA $\cdot$ min^{-1} with no decompression stops. On reaching 1 ATA, they were put into Panepinto slings to receive treatment, and monitors were attached to measure heart rate (HR) and hemoglobin saturation (VetOx 4404, Heska, Ft. Collins, CO). Because of their small particle size (approximately 0.2 μm), PFC emulsions are known to be taken up in pulmonary macrophages in swine and other cloven-hooved animals and to cause a transient increase in mean pulmonary arterial pressure (7). Therefore, the animals were given a 1 mg $\cdot$ kg^{-1} dose of methylprednisolone (MP) IV to attenuate this thromboxane-mediated response. One of the three animals was randomly selected to receive MP alone and was then put into an observation pen open to room air (air group, n = 15, mean age 48 $\pm$ 3 days, mean predive mass 21.2 $\pm$ 0.4 kg, and mean body mass loss 1.4 $\pm$ 0.2 kg, $\pm$ 1 SEM). Another of the animals received the MP and was placed into a box continuously flooded with 100% O_2 (O_2 group, mean age 48 $\pm$ 3 days, mean predive mass 21.2 $\pm$ 0.4 kg, and mean body mass loss 1.3 $\pm$ 0.1 kg, $\pm$ 1 SEM). The third animal in each dive received the MP followed by 6 ml $\cdot$ kg^{-1} (3.6 g PFC $\cdot$ kg^{-1} Oxygent™) of PFC IV over 2 min, and was then placed into a 100% O_2 environment for observation (PFC group, mean age 49 $\pm$ 3 days, mean predive mass 21.4 $\pm$ 0.4 kg, and mean body mass loss 0.8 $\pm$ 0.2 kg).

Onset of severe DCS (neurological or cardiopulmonary dysfunction) was recorded to the nearest minute by a dedicated observer blinded to treatment. Disease and symptom onset times were referenced to the time animals reached 1 ATA. The mean time the animals reached the observation pens was 4 min, and the O_2 boxes reached > 90% O_2 at a mean of 7.5 min.

Neurological DCS was defined as motor weakness (diminished limb strength, repeated uncoordinated motor activity, or inability to stand after being righted by the investigator), paralysis (complete limb dysfunction, areflexia, hypotonia), or cranial nerve dysfunction (nystagmus, prolonged fixed gaze, nonconjugate gaze). Cardiopulmonary DCS was defined as the inability to maintain normal hemoglobin saturation despite vigorous physiologic compensatory efforts, specifically, observed respiratory rate > 60 breaths $\cdot$ min^{-1}, HR > 150 beats $\cdot$ min^{-1}, and SpO$_2$ < 80% sustained for a full minute or more. This condition was usually accompanied by respiratory distress, as evidenced by open-mouthed, labored breathing, central cyanosis, inversion of the normal inspiratory/expiratory ratio, and production of frothy white sputum. All subjects with signs of severe DCS (neurological or cardiopulmonary) were given 2.5 mg diazepam IV in their observation pens as necessary to alleviate their distress. Skin DCS and behavioral features (e.g., limb lifting) indicative of milder DCS were noted, but not classified as positive cases for this study. Animals that died from their DCS were immediately weighed and sent for necropsy after recording the time of death. Animals that survived the decompression and observation period were euthanized with intravenous injection of a barbiturate solution (Euthasol®, Delmarva Laboratories, Inc., Midlothian, VA).

Analysis: To define important covariates that affected the outcome, multivariate logistic regression techniques (10) were used. This analysis determined the probability of DCS using DCS outcome (1 for DCS and 0 for no DCS) as the dependent variable and four experimental variables (age, predive weight, weight loss, and treatment group) as independent variables. Initially, a univariate analysis on each independent variable was performed in an attempt to locate those covariates that had significant effect on the outcome. Only those variables with a p-value < 0.20 (Wald test, 10) were then included in a multivariate analysis. Exclusion of an independent variable from the multivariate logistic regres-

TABLE I. GROUP, TOTAL NUMBER OF ANIMALS (n), TOTAL NUMBER OF DCS CASES (nDCS), THE DISTRIBUTION BETWEEN DIFFERENT SYMPTOMS (DCS), AND NUMBER OF DEATHS (N DIED) FOR EACH OF THE TREATMENT GROUPS.

Group	n	n DCS	DCS CNS	DCS CP	DCS Both	n Died
Control/Air	27	25	3	8	14	14
O_2	15	14	4	6	4	6
PFC	15	8	—	8	—	4
Σ	57	47	7	22	18	24

n is the number of animals in a specified group; DCS = number of animals diagnosed with severe decompression sickness, divided into isolated central nervous system cases (CNS), cardiopulmonary cases (CP), or cases with both CNS and CP manifestations. Σ is the sum total for all groups.

sion analysis was based on the log-likelihood ratio test (10).

As the symptom onset time and time of death were of interest, comparisons of DCS-free survival times and time of death in the PFC, O_2, and control/air groups were examined by Kaplan-Meier survival analysis. Log-rank testing was used to analyze for significant differences in symptom onset time and time of death between the groups. Analysis of variance (ANOVA) with Bonferroni multiple comparison testing was used when more than two populations were compared. Acceptance of significance was set to the $p < 0.05$ level, unless otherwise stated.

RESULTS

Logistic regression analysis showed that there was a significant difference in the DCS incidence between groups ($\chi^2 = 5.89$, $p < 0.05$) but no difference in the mortality rate ($\chi^2 = 0.56$, $p > 0.4$). To increase the power of the analysis, animals in the air, O_2, and PFC groups

were compared with an earlier group of 12 untreated controls (control group, mean age 68 ± 2 days, predive mass 19.7 ± 0.4 kg, and body mass loss 0.8 ± 0.1 kg) obtained from the same source and exposed to the same dive/decompression profile (4). Multivariate logistic regression analysis revealed that the DCS or death outcome of the control (DCS incidence 11/12 animals, death incidence 7/12) and air (DCS incidence 14/15 animals, death incidence 7/15) groups were not significantly different (DCS, $\chi^2 = 0.03$, $p > 0.8$; death, $\chi^2 = 0.36$, $p > 0.5$) and were, therefore, pooled for analysis (control/air group).

Table I summarizes the DCS distribution and onset. For analysis of candidate independent variables as significant predictors of DCS incidence or death, animal age, predive weight, weight loss during the dive (a surrogate for fluid losses in this model), and treatment group were tested (Table II). Control/air animals were about 9 d older than the animals in the O_2 and PFC groups ($p = 0.04$ and 0.07, respectively), but age was not a significant factor in outcome (Table II). There were no significant differences in predive weight or weight loss between the groups ($p > 0.5$, ANOVA).

Of all the animals, 82% (47/57) developed severe DCS (mean time 14.6 min $\pm$ 1.33 SEM). Animals in the PFC group sustained only 53% DCS (8/15), compared to 93% for both the O_2 (14/15) and the control/air groups (25/27; Table I). PFC treatment lowered the incidence of severe DCS in this model by nearly 50% ($p < 0.01$, logistic regression; Table II).

There was a significant difference in the DCS onset time for the three groups ($p < 0.01$, global log rank test). There was no difference between the O_2 and control/air groups ($p > 0.2$, log rank test). There was a significant difference between either the control/air or the O_2 groups vs. the PFC group ($p < 0.01$), with longer onset time for the PFC group (Fig. 1). Of the animals, 42% (24/57) died from their disease (mean time 20.1 min

TABLE II. RESULTS OF LOGISTIC REGRESSION ANALYSIS FOR AGE (DAYS), INITIAL BODY MASS (INITIAL Mb, KG), BODY MASS LOSS (Mb LOSS, KG), AND TREATMENT GROUP AS COMPARED TO CONTROL ANIMALS VERSUS DECOMPRESSION SICKNESS (DCS) OR DEATH OUTCOME.

Model	intercept	Parameter Age (d)	Parameter Initial Mb	Parameter Mb loss	Parameter Grp: O_2	Parameter Grp: PFC	LL	P
$NULL_{DCS}$	1.6 ± 0.4						-26.47	
DCS1	1.2 ± 1.3	0.006 ± 0.025					-26.44	>0.5
DCS2	3.9 ± 4.8		-0.1 ± 0.2				-26.34	>0.5
DCS3	0.9 ± 0.6			0.7 ± 0.5			-25.67	>0.1
DCS4	2.5 ± 0.7				0.1 ± 1.3	$*-2.4 \pm 0.9$	-21.17	<0.01*
DCS5	2.3 ± 1.0			0.2 ± 0.6	0.1 ± 1.3	$*-2.3 \pm 0.9$	-21.10	>0.5
$NULL_{DEATH}$	-0.3 ± 0.3						-38.80	
Death1	-1.7 ± 1.1	0.02 ± 0.02					-37.94	>0.1
Death2	3.8 ± 3.7		-0.2 ± 0.2				-38.17	>0.25
Death3	-0.6 ± 0.5			0.3 ± 0.4			-38.54	>0.25
Death4	0.07 ± 0.38				-0.5 ± 0.7	-1.1 ± 0.7	-37.49	>0.25
Death5	-1.0 ± 1.2	0.02 ± 0.02			-0.3 ± 0.7	-0.9 ± 0.7	-37.03	>0.40

*Significant parameters are those that differ from 0 with $p < 0.05$; significant models are those with $p < 0.05$ by likelihood ratio testing. For the NULL model, which is an intercept-only model and the simplest description to the data, a single parameter was generated. One NULL model was generated for each outcome. Parameter estimates $\pm$ SEM, log likelihood (LL), and p-value for log likelihood ratio test compared to nested models (10). Models (DCS1–5 and Death 1–5) include all independent variables with a parameter estimate on the same row, i.e., DCS1 contains an intercept and Age. Models DCS1–3 and Death 1–4 are univariate analyses that determine the significance of each covariate. Models DCS4–5 and Death 4–5 are the multivariate versions, where parameters are added to the model depending on the level of significance determined in the univariate analysis.
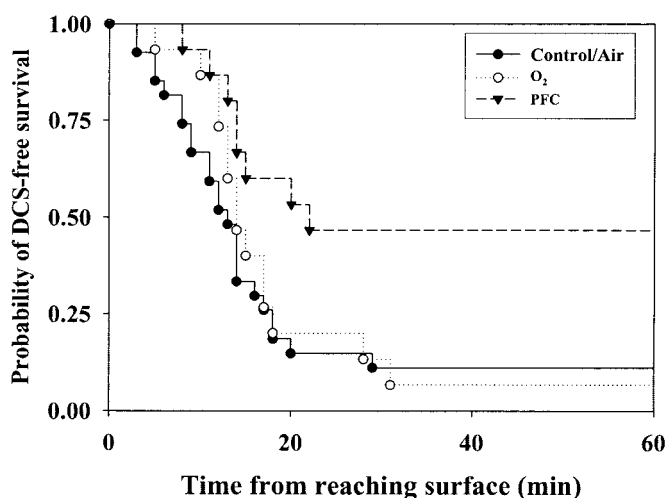
Fig. 1. Kaplan-Meier analysis of the probability of DCS-free survival in control/air, O_2, and PFC-treated Yorkshire swine for 60 min after reaching the surface following decompression from 4.9 ATA for 22 h on air.

± 1.09 SEM). There were no significant differences in the incidence of mortality (p > 0.2, logistic regression; Table II) or in the time to event between the PFC, air/control, and O_2 groups for death (p < 0.3, global log rank; **Fig. 2**).

DISCUSSION

Outcome criteria in this study were necessarily severe. The outcomes of interest in this study were chosen to assess neurological and cardiopulmonary compromise, the disease entities most likely to cause long-term disability or mortality from DCS. Use of more invasive and, therefore, more sensitive testing methods was precluded by the need to observe the untreated natural history of the disease. This was in turn prompted by the very real possibility that adequate rescue and hyperbaric assets may not be available at a disabled submarine site, as evidenced in the recent loss of the Russian submarine Kursk. Other acute events that could benefit from rapid pharmacological PFC intervention include explosive decompression in hypobaric environments.

Swine are a suitable large-animal model due to their well-recognized anatomical and physiologic similarity to humans (12,19). The pathological findings of livid skin DCS, multiple punctate spinal and cerebral hemorrhages, and profuse pulmonary congestion after no-stop decompression are consistent with previous observations in other animal models of DCS, as well as human results (1,3,20).

PFC treatment performed exceptionally well, as indicated by the fact that we found a statistically significant reduction in severe DCS and no neurological DCS (Table I). Our reduction in DCS incidence was smaller than that previously observed (10,19) for several reasons. First, prior studies used smaller animals (<1 kg) with a larger relative dose of PFC (4–10 g PFC · kg^{-1} body weight as opposed to 3.6 g PFC · kg^{-1} body weight in our study). The animals were also sedated for observation (11,18). We set out to simulate a worst-case rescue situation rather than ideal laboratory conditions, so our

animals were awake and, therefore, able to react to their insult. The stress response places additional demands on the cardiovascular system. Also, in previous work, the sedated animals were immediately connected to a tight fitting facemask delivering 100% O_2. Again, because we were trying to simulate a rescue situation, there was a delay before the animals' breathing medium reached 100% O_2. One might expect that outcome could be further improved with modern critical care interventions and invasive monitoring, but one must question the immediate availability of such assets in emergency situations, as well as the feasibility of using them when mass casualty situations occur in remote locations.

The present study showed that the therapeutic effects of intravenous PFC emulsion significantly lowered DCS onset in larger conscious animals possessing lower metabolic and gas exchange rates. If one considers the neurological and cardiopulmonary outcomes separately (Table I), there was an indication of a protective effect against cardiopulmonary DCS (8/15 in the PFC group vs. 32/42 in the combined control groups (χ^2 test, p < 0.10). The more impressive finding was the complete lack of central nervous system manifestations in the PFC group (Table I). This finding bodes well for use of this compound to combat isolated central nervous system pathology in situations where hyperbaric treatment is delayed or unavailable. Using a one sided χ^2 test, there was a significant difference in the mortality rate between the PFC and the control/air group (p < 0.05, Table I). Alternatively, PFC intervention may only successfully reduce DCS risk if the total gas burden is relatively low and the decompression rate is fairly slow. Thus, additional studies are necessary to further explore the possibility of using PFC as an adjunctive DCS treatment.

The MP was given because PFC emulsion has shown a species-specific transient increase in pulmonary arterial pressure in swine (7), and increases in pulmonary arterial pressure are a known part of the pathophysiology of massive venous gas embolism (13). Without
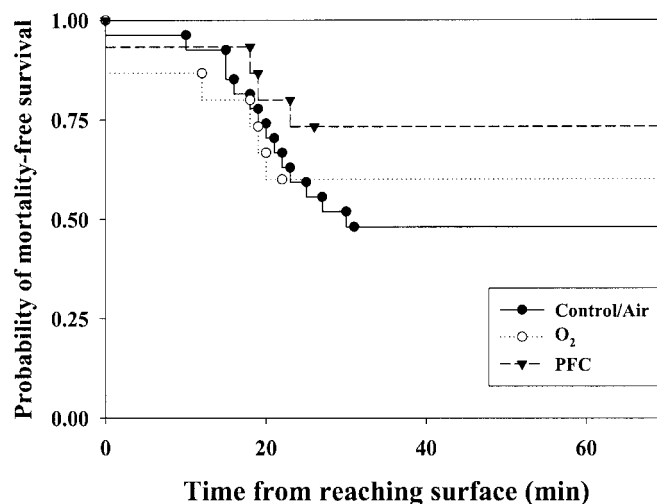

Fig. 2. Kaplan-Meier analysis of the probability of mortality-free survival in control/air, O_2, and PFC-treated Yorkshire swine for 60 min after reaching the surface following decompression from 4.9 ATA for 22 h on air.

central venous monitoring we cannot confirm that the MP fully prevented this, but such monitoring was specifically avoided as it is suspected to provide a nidus for bubble formation and, therefore, alter the natural history of the disease process. However, there is no evidence the MP significantly altered outcome since the air and O$_2$ groups were clinically and statistically indistinguishable from untreated controls. The effect of PFC emulsion (which contains no added colloid) is not due to intravascular volume expansion alone. Volume expansion with colloid in prior experiments (18,19) was not effective, and previous experiments (unpublished data) with crystalloid infusion in this animal model have actually increased the DCS incidence, presumably by contributing to the non-cardiogenic pulmonary edema that comes from massive venous gas embolism and subsequent endothelial stripping.

In summary, intravenous PFC emulsion treatment was effective in treating decompression sickness in the large animal model in the present study, even when purposely used in less than ideal circumstances against severe DCS insult. The present study shows that administered with 100% oxygen, the PFC emulsion was significantly more effective than other pharmacological intervention thus tested. By altering the solubility coefficient for non-polar gases in plasma, PFC temporarily increases the N$_2$ carrying capacity of the blood, which allows modification of the decompressive insult. Whether the beneficial effects are from inert gas removal alone or from improved O$_2$ delivery to hypoxic tissues remains to be conclusively demonstrated. However, the process called H$_2$-biochemical decompression has been shown to successfully reduce DCS incidence in a swine model by active removal of the inert gas. Furthermore, probabilistic modeling suggested that elimination of relatively small fractions of dissolved gas may have a surprisingly large impact on the DCS incidence (5). This concurs with the idea that at least a portion of the beneficial effects of PFC treatment stems from removal of the inert gas dissolved in the tissues. Future work should determine whether PFC emulsions exert their effect by increased O$_2$ delivery to hypoxic tissues or by reduction of bubble load, as well as how this effect is influenced by hyperbaric treatment and changes in ambient breathing mixture. It is important to note, however, that severe DCS still occurred in the treated group. The authors emphasize that no data suggests that PFC infusion can adequately substitute for formal hyperbaric therapy.

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